CLAIMS

What is claimed is:

1. A phosphodiesterase 1B (PDE1B) crystal.

2. The PDE1B crystal of claim 1 which is derived from a mammal.

3. The PDE1B crystal of claims 2 comprising SEQ ID NO:1, or a homologue or variant thereof.

4. A crystal of a PDE1B/PDE1B ligand complex.

5. The crystal complex of claim 4 wherein said ligand is an antagonist or an inhibitor.

6. A crystal complex comprising a polypeptide with an amino acid sequence spanning amino acids Thr142 to Gln507 listed in SEQ ID NO:1, or a homologue or variant thereof.

7. The crystal complex of claim 6, wherein the homologue or variant has an amino acid identity of at least 98%, 95%, 90%, 85%, 80%, or 75% with a polypeptide having an amino acid sequence spanning amino acids Thr142 to Gln507 listed in SEQ ID NO:1.

8. The crystal complex of claim 7, wherein said crystal further comprises compound 109 and said crystal has the atomic coordinates listed in FIG. 4.

9. The crystal complex of claim 6, wherein the homologue or variant thereof has a protein backbone comprising the atomic coordinates, or portions thereof, that are within a root mean square of +/- 2.0, 1.7, 1.5, 1.2, 1.0, 0.7, 0.5, or even 0.2 Å of the atomic coordinates, or portions thereof, listed in FIG. 4.

10. A polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1 or a homologue or variant thereof, wherein the molecules are arranged in a crystalline manner belonging to space group $P4_32_12$ with unit cell dimensions a=87.47 Å, b=87.47 Å, c=135.03 Å, $\alpha=\beta=\gamma=90.0°$, and which effectively diffracts X-rays for determination of the atomic coordinates of PDE1B polypeptide to a resolution of about 1.8 Å.

11. A polypeptide consisting essentially of the catalytic domain of PDE1b.

12. A computer for producing a three-dimensional representation of a polypeptide with an amino acid sequence spanning amino acids Thr142 to Gln507 listed in SEQ ID NO:1, or a homologue, or a variant thereof comprising:

a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of FIG. 4, or portions thereof;

a working memory for storing instructions for processing said computer-readable data;

a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-machine readable data into said three-dimensional representation; and

a display coupled to said central-processing unit for displaying said representation.

13. A computer for producing a three-dimensional representation of a molecule or molecular complex comprising the atomic coordinates in FIG. 4 comprising:

a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of FIG. 4, or portions thereof;

a working memory for storing instructions for processing said computer-readable data;

a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-machine readable data into said three-dimensional representation; and

a display coupled to said central-processing unit for displaying said representation.

14. A computer for producing a three-dimensional representation of a molecule or molecular complex comprising the atomic coordinates having a root mean square deviation of less than 2.0, 1.7, 1.5, 1.2, 1.0, 0.7, 0.5, or 0.2 Å from the atomic coordinates for the carbon backbone atoms listed in FIG. 4 comprising:

a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of FIG. 4, or portions thereof;

a working memory for storing instructions for processing said computer-readable data;

a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-machine readable data into said three-dimensional representation; and

a display coupled to said central-processing unit for displaying said representation.

15. A computer for producing a three-dimensional representation of a molecule or molecular complex comprising a binding site defined by the structure coordinates in FIG. 4, or a the structural coordinates of a portion of the residues in FIG. 4, or the structural coordinates of one or more PDE1B amino acids in SEQ ID NO:1 selected from His223, His373, Thr385, Leu388, Ser420, Gln421, and Phe424, wherein said computer comprises:

a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of FIG. 4, or portions thereof;

a working memory for storing instructions for processing said computer-readable data;

a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-machine readable data into said three-dimensional representation; and

a display coupled to said central-processing unit for displaying said representation.

16. The PDE1B crystal of claim 1 having the atomic coordinates set out in FIG. 4, or a derivative expressed in any reference frame.

17. A method for generating the 3-D atomic coordinates of protein homologues of PDE1B using the X-ray coordinates of PDE1B described in FIG. 4, said method comprising:

identifying the sequences of one or more proteins which are homologues of PDE1B;

aligning the homologue sequences with the sequence of PDE1B (SEQ ID NO:1);

identifying structurally conserved and structurally variable regions between the homologue sequences, and PDE1B (SEQ ID NO:1);

generating 3-D coordinates for structurally conserved residues, variable regions and side-chains of the homologue sequences from those of PDE1B; and

combining the 3-D coordinates of the conserved residues, variable regions and side-chain conformations to generate a full or partial 3-D coordinates for said homologue sequences.

18. A method for identifying a potential ligands for PDE1B, or homologues, analogues or variants thereof, comprising the steps of:

displaying three dimensional structure of PDE1B enzyme, or portions thereof, as defined by atomic coordinates in FIG. 4, on a computer display screen;

optionally replacing one or more PDE1B enzyme amino acid residues listed in SEQ ID NO:1, or one or more of the amino acids listed in Tables 1-3, or one or more amino acid residues selected from His223, His373, Thr385, Leu388, Ser420, Gln421, and Phe424, in said three-dimensional structure with a different naturally occurring amino acid or an unnatural amino acid;

employing said three-dimensional structure to design or select said ligand;

contacting said ligand with PDE1B, or variant thereof, in the presence of one or more substrates; and

measuring the ability of said ligand to modulate the activity PDE1B.

19. The method of claim 18 further comprising the steps of:

computationally modifying the structure of the ligand; and

computationally determining the fit of the modified ligand with the three-dimensional coordinates of PDE1B set forth in FIG. 4, or portions thereof.

20. A method for treating psychological disorders comprising administering to a patient in need of treatment the pharmaceutical compositions of ligands identified by structure-based drug design using the atomic coordinates substantially similar to, or portions of, the coordinated listed in FIG. 4.

21. The method of claim 20, wherein the psychological disorders are selected from multiple variants of schizophrenia, anxiety disorders, movement disorders selected from Huntington's disease, Parkinson's disease and dyskinesia, alcohol and drug addictions, cognitive deficiencies, and mood disorders.

22. An expression vector useful in a method for preparing a purified catalytic domain of PDE1B comprising a polypeptide with an amino acid sequence spanning amino acids Thr142 to Gln507 listed in SEQ ID NO:1, or a homologue or variant thereof.